SETD7 Drives Cardiac Lineage Commitment through Stage-Specific Transcriptional Activation.

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Public Summary:

Scientific Abstract:
Cardiac development requires coordinated and large-scale rearrangements of the epigenome. The roles and precise mechanisms through which specific epigenetic modifying enzymes control cardiac lineage specification, however, remain unclear. Here we show that the H3K4 methyltransferase SETD7 controls cardiac differentiation by reading H3K36 marks independently of its enzymatic activity. Through chromatin immunoprecipitation sequencing (ChIP-seq), we found that SETD7 targets distinct sets of genes to drive their stage-specific expression during cardiomyocyte differentiation. SETD7 associates with different co-factors at these stages, including SWI/SNF chromatin-remodeling factors during mesodermal formation and the transcription factor NKX2.5 in cardiac progenitors to drive their differentiation. Further analyses revealed that SETD7 binds methylated H3K36 in the bodies of its target genes to facilitate RNA polymerase II (Pol II)-dependent transcription. Moreover, abnormal SETD7 expression impairs functional attributes of terminally differentiated cardiomyocytes. Together, these results reveal how SETD7 acts at sequential steps in cardiac lineage commitment, and they provide insights into crosstalk between dynamic epigenetic marks and chromatin-modifying enzymes.

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